

that may eventually allow us to greatly enhance our knowledge of prognostic and predictive biomarkers for the use of EGFR antibodies. I hope this will benefit our patients with improved future therapies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory**

Role: None **Stock Ownership:** None **Honoraria:** None **Research**

Funding: Axel Grothey, Genentech, Bayer Pharmaceuticals **Expert**

Testimony: None **Other Remuneration:** None

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DOI: 10.1200/JCO.2010.29.3407; published online ahead of print at www.jco.org on October 4, 2010

Cancer Vaccines in Glioma: How to Balance the Challenges of Small Trials, Efficiency, and Potential Adverse Events

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See accompanying article on page 4722

High-grade glioma tumors (glioblastoma multiforme WHO grade 4) continue to carry a dire prognosis, although median survival is slowly increasing. In the most recent clinical trials in high-complexity US centers, median survival is inching toward 18 to 21 months, up from 15 months in earlier trendsetting trials that showed temozolomide to be an effective addition to the standard of care of surgical resection followed by radiotherapy.¹⁻⁸ Nevertheless, even with optimized use of temozolomide, complete surgical resection, and radiotherapy, long-term survival remains elusive. Thus, novel therapeutic approaches are being explored, and Sampson et al⁹ report in this

issue of *Journal of Clinical Oncology* that a vaccine against a glioma antigen provides a survival advantage in a phase II trial when compared with a cohort of contemporaneous patients.

The difficulties of performing large-scale clinical trials with high-grade glioma were recently highlighted by a large, multicentric, randomized, controlled, double-blind phase III European trial testing the effectiveness of gene therapy by using adenoviral vectors that expressed herpes simplex virus 1 thymidine kinase followed by ganciclovir to kill dividing glioma cells as an addition to standard of care conducted by Ark Therapeutics (London, United Kingdom).^{10,11}

Because the trial was performed at many European clinical centers, differences in the standard of care across different countries made the assessment of any potential benefits of the addition of gene therapy extremely complicated. When presented with all the clinical data, the European Medicines Agency's Scientific Advisory Group on Oncology did not approve commercialization of this otherwise promising therapy at this stage. The reasons given were that the agency did not consider the current study to provide sufficient evidence of clinical benefit, and the company was advised that it must conduct a further study to show a benefit for an end point that is clinically and statistically robust.¹²⁻¹⁴

Because of the spread of metastatic tumors, there remains high enthusiasm for stimulating the immune system to seek and destroy target tumor cells and improve median survival. Thus, excitement for tumor vaccination approaches received a recent boost with the US Food and Drug Administration's approval of sipuleucel-T (Provenge; Dendreon, Seattle, WA) immunotherapy for the treatment of castration-resistant prostate cancer.¹⁵ The improved survival of 4 months for those receiving the active immunization compared with controls was not accompanied by a measurable antitumor effect; only one of 341 patients had a partial tumor response, and 10 patients had a 50% reduction in prostate specific antigen values. At an estimated total cost of \$93,000 (or \$23,000 per month of survival advantage with a 4-month median increased survival) compared with conventional standard of care costs of \$1,800 per month, the treatment is more likely to be used in the United States than in other health systems. The essential challenge in evaluating ongoing vaccination trials is that the numbers of patients receiving treatment is small, the results are limited, and objective responses are unavailable, even when a statistically significant survival improvement is detected. Nevertheless, the importance of the sipuleucel-T trial was that it achieved a statistically significant improvement in a randomized phase III trial—the gold standard of clinical trials.¹⁶ Its true clinical impact in the long-term treatment of castration-resistant prostate cancer will be revealed with continued clinical use and experience.

The panorama of immune strategies for the treatment of high-grade glioma tumors is not much simpler to evaluate. Different immune-therapeutic approaches have been tested preclinically and are currently in evaluation in early phase I and II trials. Approaches vary from the use of autologous dendritic cells loaded with tumor peptides removed from the patients' own tumors¹⁷⁻²² to autologous dendritic cells loaded with synthesized potential tumor antigenic peptides²³⁻³⁰ to the use of autologous and/or allogeneic T cells engineered or selected to recognize potential glioma antigens.³¹⁻³⁶ Dendritic cells are usually given as vaccines to a peripheral site, whereas T cells are either delivered systemically or into the resection cavity of the brain tumor.

Results from these trials vary, but the overall increased survival benefit obtained so far has been limited. Interestingly, although there is a potential to stimulate brain autoimmune responses as normal brain antigens are likely to be present among the peptides used to load dendritic cells, no such autoimmune responses or brain inflammation has been detected in most trials.³⁷⁻³⁹ The lack of autoimmune adverse effects has usually been taken to indicate the safety of the dendritic cell vaccination approach. Conversely, it could also mean a lack of efficient immunization in patients with high-grade glioma, a population of patients already known to display systemic immune suppression. In comparison, when patients with Alzheimer's were immunized systemically against β -amyloid peptides, 10% to 15% developed clinically significant brain inflammation, which led to a suspension of the

ongoing trial.⁴⁰ Given that systemic immunization against brain antigens ought to lead to significant brain autoimmunity in at least a percentage of patients, the absence of such responses from glioma immunotherapy trials requires further examination.

Existing tumor antigens have been proposed to serve as targets for immunotherapies. A percentage of glioma tumors express a truncated variant of EGFR, known as EGFRvIII,^{26,41,42} which promotes ligand-independent signaling. If EGFRvIII is indeed a driver of gliomas, directly attacking EGFRvIII and destroying glioma cells that express EGFRvIII ought to provide a therapeutic benefit. To this end, Sampson et al⁹ report the use of vaccination against a peptide derived from the mutated EGFR. They describe the results of a phase II non-randomized multicenter trial in which a group of 18 patients who received treatment was compared with a contemporaneous group of patients who did not receive treatment. The authors report an improved progression-free survival of 6 months and improved overall survival (OS); the median OS was 15 months in a contemporaneous, matched cohort compared with 26 months in the immunized cohort.

To understand the mechanisms of action in their trial, Sampson et al studied a variety of immunologic measures. Their results indicate that, in patients whose tumors are EGFRvIII positive at initial resection, an immune response can be stimulated by using the techniques described by the authors in approximately 50% of tumors. Of 17 patients who were immunized, six developed EGFRvIII antibodies, and three developed evidence of a T-cell response against EGFRvIII. Interestingly, the development of either a humoral or a cellular response to the EGFRvIII peptide appeared to be associated with increased OS, although the small numbers did not allow detailed statistical analysis.

In addition, the authors examined EGFRvIII expression at tumor recurrence. In 11 patients who could have tumor samples evaluated both before and after vaccination, 82% of tumors lacked EGFRvIII immunoreactivity at recurrence. The authors favor the interpretation that this indicates tumor escape, although it is impossible, at this stage, to differentiate tumor escape from loss of immunoreactivity as a result of the blocking of endogenous EGFRvIII immunoreactivity by the induced anti-EGFRvIII antibodies or downregulation of EGFRvIII expression. Although the clinical progression of the disease would support an interpretation of effective tumor control by the immunization followed by tumor mutation and escape, the absence of more detailed molecular studies and the low number of subjects involved preclude drawing definitive conclusions. One would prefer to analyze results from large-scale, randomized, double-blind, phase III trials; however, it could be challenging to recruit a sufficient number of patients with brain tumors immunoreactive for EGFRvIII. In any case, the studies warrant future immunizations against a combination of tumor peptides to avoid or reduce the potential of tumor antigenic escape.

Sampson et al⁹ demonstrate that 33% of patients who were immunized developed humoral responses, whereas 16% developed cellular responses. Should the next step be a phase III trial, or would it be possible to increase the response to immunization to larger than 50% of patients preceding a larger, phase III trial? Why did only 50% of patients respond? Could this be a result of the general immune-suppression of patients with gliomas or of technical details of immunization procedures? Are the strongest results from this trial the increase in OS in a nonrandomized trial or the induction of immune responses in 50% of patients? It would be important to understand the mechanisms underlying a significant increase in OS, even if immune responses were only detected in 50% of patients. Alternatively,

the assessment of immune responses could be delayed until a treatment is found that provides a significant OS benefit in a randomized phase III trial, such as the sipuleucel-T trial for castration-resistant prostate cancer. How are we to interpret that increased OS in the sipuleucel-T trial was seen in the absence of effects on tumor progression or even without stimulation of immune responses? In the case of brain tumors, would it be worth repeating a small trial but with an attempt to obtain direct evidence of intracranial antitumor immune reactivity, possibly by using positron emission tomography imaging? What should be the way forward for immunotherapies to cross the bar of generalized clinical implementation? The field of cancer immunotherapies needs to urgently address what to look for in such small, early, yet promising, clinical trials.

There appear to be at least two possible ways forward. One would be to concentrate on achieving increased OS without paying too much attention to progression-free survival, tumor shrinkage, or other surrogate markers of treatment efficacy—all of which have their own complex shortcomings. Once a new therapy has demonstrated a clinically significant increase in OS, then one could perform further studies on how the treatment works. The second possibility would be to simultaneously look for increases in OS and examine surrogate markers of treatment efficacy. The challenge to clinical oncology is knowing how to interpret a treatment that provides a small, yet statistically significant survival increase in the absence of compelling indications that the treatment is indeed working as expected. In the sipuleucel-T trial, the 4-month increase in survival was statistically significant, even if less than 4% of patients showed reduction in markers of tumor growth. Are such small, yet statistically significant changes of true long-term clinical relevance?

Sampson et al⁹ report an increased OS of 9 months compared with contemporaneous controls. If a comparable difference could be maintained in a larger randomized trial, the use of the EGFRvIII vaccine in suitable patients would be amply justified. The challenge remains how to determine the rational use of EGFRvIII vaccine in the absence of a large, randomized, double-blind, controlled, phase III trial. Thus, it is important to explore alternatives to study small clinical trials in detail. For example, it would be feasible to perform further small clinical trials that would compare various immunotherapeutic approaches against each other and to analyze these trials by using either adaptive trial designs or Bayesian designs that simultaneously evaluate efficacy and toxicity.

The clinical challenge remains how to assess whether small survival benefits are indeed clinically significant to reassure all stakeholders that the benefit is not a result of inadvertent bias. In other cases (eg, at the early stages of treatment for childhood leukemias), it was possible to determine whether, even in the absence of long-term remissions, anticancer agents displayed temporary reductions in the proliferation of neoplastic cells. Such small, yet clinically significant, effects led to further improvements, which led to the ultimate reduction in the morbidity and mortality of diseases such as childhood leukemias after years of continued research. It remains the responsibility of clinicians, oncologists, neurosurgeons, neuroradiologists, and basic scientists involved in glioma research to advance our statistical, oncologic, and clinical assessment of small clinical trials to achieve large therapeutic-effect sizes that will benefit the patient community as a whole by extracting as much clinically relevant information as possible to separate true treatment effects from inadvertent experimental bias and artifacts.^{4,3}

AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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DOI: 10.1200/JCO.2010.32.1117; published online ahead of print at www.jco.org on October 4, 2010

STATEMENT OF OWNERSHIP MANAGEMENT AND CIRCULATION (Required by 39 U.S.C. 3685)

1. Publication title: JOURNAL OF CLINICAL ONCOLOGY.
2. Publication no.: 0732-183X.
3. Filing date: October 1, 2010.
4. Issue frequency: 36 times/year; 3 times/month.
5. No. of issues published annually: 36.
6. Annual subscription price: \$578.00.
7. Complete mailing address of known office of publication: 2318 Mill Road, Suite 800, Alexandria, VA 22314-4609.
8. Complete mailing address of the headquarters or general business offices of the publisher: 2318 Mill Road, Suite 800, Alexandria, VA 22314-4609.
9. Full names and complete mailing addresses of publisher, editor, and managing editor: Publisher: Theresa Van Schaik, Publisher, Journal of Clinical Oncology, 2318 Mill Road, Suite 800, Alexandria, VA 22314-4609 Editor: Daniel G. Haller, MD, Editor-in-Chief, Journal of Clinical Oncology, University of Pennsylvania Cancer Center, 3600 Spruce Street, 6 Penn Tower, Philadelphia, PA 19104-4211. Managing Editor: Kenneth G. Kornfield, Managing Editor, Journal of Clinical Oncology, 2318 Mill Road, Suite 800, Alexandria, VA 22314. Owner: American Society of Clinical Oncology, 2318 Mill Road, Suite 800, Alexandria, VA 22314-4609.
10. Known bondholders, mortgagees, and other security holders owning or holding 1 percent or more of total amount of bonds, mortgages, or other securities: None.
11. Purpose, function, and nonprofit status: Has not changed during preceding 12 months.
12. Publication title: JOURNAL OF CLINICAL ONCOLOGY.
13. Issue date for circulation data: Volume 27, Issue 27 (September 20, 2009).
14. Extent and nature of circulation: Average number of copies each issue during preceding 12 months: (a) Total no. copies (net press run), 25,238. (b) Paid and/or requested circulation: (1) Paid/requested outside-county mail subscriptions stated on Form 3541 (include advertiser's proof and exchange copies): 10,389; (2) Paid in-county subscriptions stated on Form 3541 (include advertiser's proof and exchange copies): N/A; (3) Sales through dealers and carriers, street vendors, counter sales, and other non-USPS paid distribution: 7,450; (4) Other classes mailed through the USPS: N/A. (c) Total paid and/or requested circulation (sum of 15b(1)-15b(4)): 17,840. (d) Free distribution by mail (samples, complimentary, and other free): (1) Outside-county as stated on Form 3541: 376; (2) In county as stated on Form 3541: N/A; (3) Other classes mailed through the USPS: N/A. (e) Free distribution outside the mail (carriers or other means): 113. (f) Total free distribution (sum of 15d and 15e): 489. (g) Total distribution (sum of 15c and 15f): 18,328. (h) Copies not distributed: 6909. (i) Total (sum of 15g and 15h): 25,237. (j) Percent paid and/or requested circulation (15c/15g x 100): 97.81%. Actual no. copies of single issue published nearest to filing date: (a) Total no. copies (net press run): 24,550. (b) Paid and/or requested circulation: (1) Paid/requested outside-county mail subscriptions stated on Form 3541 (include advertiser's proof and exchange copies): 14,507; (2) Paid in-county subscriptions stated on Form 3541 (include advertiser's proof and exchange copies): N/A; (3) Sales through dealers and carriers, street vendors, counter sales, and other non-USPS paid distribution: 7,385; (4) Other classes mailed through the USPS: N/A. (c) Total paid and/or requested circulation (sum of 15b(1)-15b(4)): 22,831. (d) Free distribution by mail (samples, complimentary, and other free copies): (1) Outside-county as stated on Form 3541: 386 (2) In-county as stated on Form 3541: N/A; (3) Other classes mailed through the USPS: N/A. (e) Free distribution outside the mail (carriers or other means): 147. (f) Total free distribution (sum of 15d and 15e): 533. (g) Total distribution (sum of 15c and 15f): 23,364. (h) Copies not distributed: 1186. (i) Total (sum of 15g and 15h): 24,550. (j) Percent paid and/or requested circulation (15c/15g x 100): 97.33%.
15. This Statement of Ownership will be printed in Volume 28, Issue 31 (November 1, 2010).
16. I certify that the statements made by me above are correct and complete.

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